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Infectobesity: obesity of infectious origin.

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In the U.S., the prevalence of obesity increased by 30% from 1980 to 1990, and this increase appears to be continuing. Although obesity has multiple etiologies, an overlooked possibility is obesity of an infectious origin. Six pathogens are reported to cause obesity in animals. Canine distemper virus was the first virus reported to cause obesity in mice, followed by Rous-associated virus-7, an avian retrovirus, which has been shown to cause stunting, obesity and hyperlipidemia in chickens. Next, the obesity-promoting effect of Borna disease virus was demonstrated in rats. Scrapie agents were reported to induce obesity in mice and hamsters. The final two reports were of SMAM-1, an avian adenovirus, and Ad-36, a human adenovirus that caused obesity in animals. Additionally, an association with human obesity is the unique feature of SMAM-1 and Ad-36. Although the exact mechanism of pathogen-induced obesity is unclear, infection attributable to certain organisms should be included in the long list of potential etiological factors for obesity. In addition, the involvement of some pathogens in etiology of obesity suggests the possibility of a similar role for additional pathogens.

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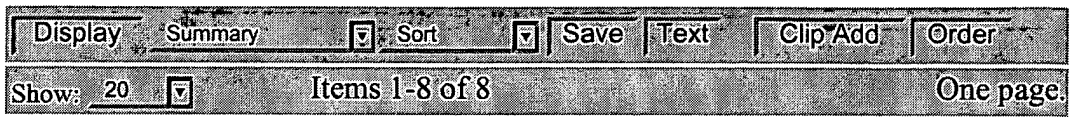

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Symposium: Emerging Role of Pathogens in Chronic Diseases Requiring Nutritional Intervention

Infectobesity: Obesity of Infectious Origin[1]

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ABSTRACT In the U.S., the prevalence of obesity increased by 30% from 1980 to 1990, and this increase appears to be continuing. Although obesity has multiple etiologies, an overlooked possibility is obesity of an infectious origin. Six pathogens are reported to cause obesity in animals. Canine distemper virus was the first virus reported to cause obesity in mice, followed by Rous-associated virus-7, an avian retrovirus, which has been shown to cause stunting, obesity and hyperlipidemia in chickens. Next, the obesity-promoting effect of Borna disease virus was demonstrated in rats. Scrapie agents were reported to induce obesity in mice and hamsters. The final two reports were of SMAM-1, an avian adenovirus, and Ad-36, a human adenovirus that caused obesity in animals. Additionally, an association with human obesity is the unique feature of SMAM-1 and Ad-36. Although the exact mechanism of pathogen-induced obesity is unclear, infection attributable to certain organisms should be included in the long list of potential etiological factors for obesity. In addition, the involvement of some pathogens in etiology of obesity suggests the possibility of a similar role for additional pathogens. J. Nutr. 131: 2794S–2797S, 2001.

KEY WORDS: • *obesity* • *infection*

Background

Obesity has been called the number one public health problem in America (1). The etiology of obesity is considered to be multifactorial. Sclafani (2) has classified the etiology of animal obesity in nine different groups, including obesity of neural, endocrine, pharmacological, nutritional, environmental, seasonal, genetic, idiopathic or of viral origin. While genetic and behavioral components of obesity have been the focus of intense study, an infection as an etiological factor has received little attention. Although "infectobesity," a new term to describe obesity of infectious origin, appears to be a new concept, over the past 20 y six different pathogens have been reported to cause obesity in animal models (3–11). The relative contribution of these pathogens to human obesity is unknown.

An adequate understanding of the pathogens as etiological factors is needed for better management of obesity. A new perspective about the infectious etiology of obesity may initiate additional research in the field to assess the contribution of pathogens in human obesity and possibly to prevent or treat the obesity of infectious origin. The following is a review of the role of various pathogens that have been implicated in obesity. Two of the pathogens, avian adenovirus SMAM-1 and a human adenovirus Ad-36, have been associated with human obesity and, therefore, will be discussed in detail.

Canine distemper virus. Lyons et al. (11) published the first report of obesity induced by a virus, which showed canine distemper virus (CDV)[3], from the family of paramyxoviruses, induced obesity in mice (11). Body weight, fat cell size and fat cell number increased significantly in Swiss albino mice experimentally infected with CDV. Of the mice surviving CDV infection, hyperplastic and hypertrophic obesity was observed 6–20 wk after infection in ~26% of the animals when infected intracerebrally and in 16% of the animals when infected intraperitoneally with the virus. The obese mice had reduced circulating catecholamine levels. The phenomenon of CDV-induced obesity in mice has been subsequently confirmed and is believed to be due to virus-induced hypothalamic damage (12–15). Recently, Bernard et al. (16) showed downregulation of expression of the leptin receptor in the hypothalami of CDV-infected obese mice and suggested it as the cause of the observed weight gain. Bernard et al. (16) feel that the results demonstrate a "hit-and-run" type of relation between CDV and the expression of obesity, i.e., the initial viral impact in the hypothalamus may initiate changes that would continue to promote obesity in animals even after the acute infection has subsided. CDV is not considered a human pathogen, and the contribution of CDV to human obesity is unknown. However, measles virus is a human virus closely related to the CDV and belongs to the paramyxovirus family. Animal experiments

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[3] Abbreviations: BDV, Borna disease virus; CDV, canine distemper virus; CELO, chick embryo lethal orphan; RAV-7, Rous-associated virus-7.

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showing the effect of measles virus on adiposity are unavailable.

Rous-associated virus-7. Carter et al. (4) reported a syndrome characterized by stunting, hyperlipidemia, hypercholesterolemia and obesity due to Rous-associated virus-7 (RAV-7) infection in chickens. Inoculation of 10-d-old chick embryos with RAV-7 via a chorioallantoic route produced fat deposition around crop and abdominal fat pads in the adult birds (4). The results could be replicated by similar inoculations with the serum obtained from RAV-7–infected adult birds (5). The RAV-7–induced obesity syndrome and pathology is dependent on route of inoculation. Intravenous inoculation of 1-d-old chickens with RAV-7 did not produce stunting and obesity.

RAV-7 produced fatty and yellow-colored livers, hepatomegaly, anemia and immune suppression. The livers were 6.2 and 2.4% of the body weight in the RAV-7–infected and -uninfected birds, respectively. These disease manifestations were seen within 3–4 wk after hatching of the eggs. The stunting and hyperlipidemia were the most striking features of the syndrome observed in the RAV-7–infected chickens. The mean body weight of 50-d-old RAV-7–infected chickens was 194 g, as compared with 515 g in the age-matched control group. Several chickens from the RAV-7 group had serum triglycerides levels >2,000 mg/dL, and one chicken had serum triglycerides >14,000 mg/dL. Food intake was not different for the RAV-7–infected and -uninfected control groups. Also, dietary fat content did not influence the degree of lipid accumulation in the birds. RAV-7–infected chickens have decreased levels of thyroid hormones, which was a suggested cause of the observed obesity and hyperlipidemia (4). Although this work was done >17 y ago, its relevance to human obesity is unknown.

Borna disease virus. Borna disease virus (BDV) was the third virus to be implicated in obesity. Gosztonyi and Ludwig (17) have described in detail the pathogenesis of BDV. BDV is a single, negative-stranded RNA virus that primarily targets the nervous system but also replicates in many other organs. In nature, BDV infections occur in horses and sheep and cause encephalomyelitis, but experimental infection may be produced in birds, rodents and primates. BDV infection produces a syndrome of obesity in rats, characterized by lympho-monocytic inflammation of the hypothalamus, hyperplasia of pancreatic islets and elevated serum glucose and triglycerides (10).

Gosztonyi and Ludwig (10) state that expression of BDV-induced obesity syndrome varies with the age of the animals at the time of inoculation, the genetic background of the host and the virus strain used. Rats infected as newborns with BDV (passaged and harvested in rabbits) show progressive neurological disease after 12–16 mo. On the other hand, weanling or adult rats similarly inoculated with BDV develop acute encephalitis and die within 1–4 mo. Some of these rats survive the infection and develop marked obesity (18). BDV affects several areas in the brain, and a central mechanism is a strong possibility (perhaps due to a virus-induced hypothalamic damage). The exact mechanisms of BDV-induced obesity remain unknown.

Although BDV was not considered to be a human pathogen, BDV antigen and antibodies have been seen in humans as well (10). BDV is associated with schizophrenia and mental depression in humans (19,20), which is responsive to treatment by amantadine, an antiviral (21,22). Further research is needed to determine if BDV contributes to the depression observed in obese individuals.

Scrapie agent. Scrapie is a neurodegenerative disease of a long incubation period, known to occur in sheep and goats. Although the key features of scrapie infections are abnormal behavior and motor dysfunction, mice (23) and hamsters (24) experimentally infected with scrapie agents also developed obesity. The obesity-promoting characteristic is a function of the scrapie strain but not mouse strain. Regardless of the mouse strain tested, scrapie strain ME7 induced obesity. The effect was not observed with scrapie strains 139A or 22L (25). Vacuolation caused by ME7 is in the forebrain of the mouse, whereas, 22L and 139A cause vacuolation in the cerebellum and white matter, respectively (25). It is not known if the difference in the obesity-promoting potential of the agents is linked to the differences in the brain lesions observed. Kim et al. (26) demonstrated that adrenalectomy prevents ME7-induced obesity in mice, and suggest that scrapie-induced obesity depends on an effect of scrapie on the hypothalamic-pituitary-adrenal axis.

SMAM-1 avian adenovirus. In India, Ajinkya (27) identified SMAM-1 avian adenovirus as the cause of an epidemic that had killed thousands of poultry in India in the early 1980s. SMAM-1 is serologically similar to chick embryo lethal orphan (CELO) avian adenovirus present in the U.S. (27). Information about the presence of SMAM-1 in the U.S. is not available.

Three-week-old chickens experimentally inoculated with SMAM-1 developed excessive visceral fat and paradoxically lower levels of serum lipids compared with the uninfected controls (6,7). A third group of uninoculated chickens sharing the room with inoculated chickens (in-contact group) also developed the obesity syndrome, evidently from airborne virus particles (6,7). In addition to adiposity, the SMAM-1–infected birds developed pale and enlarged liver and kidneys, hepatic fatty infiltration and congestion, and basophilic intranuclear inclusion bodies in hepatocytes (6,7). Food intake was similar for the three groups, and the final body weight for the inoculated group was lower than that for the control group. Total carcass fat was not determined in these experiments, but the visceral fat was greater by 53 and 33% in the inoculated and in-contact groups, respectively.

Subsequently, Dhurandhar et al. (28) screened 52 obese humans for antibodies to SMAM-1 virus using agar-gel-precipitation test. Approximately 20% of the subjects had antibodies to SMAM-1. The antibody-positive subjects had significantly greater body weight (95.1 ± 2.1 vs. 80.1 ± 0.6 kg, $P < 0.02$) and BMI (35.3 ± 1.5 vs. 30.7 ± 0.6 kg/m^2, $P < 0.001$) compared with the antibody-negative group. Moreover, the SMAM-1 antibody–positive group had ~15% lower serum cholesterol and 60% lower serum triglycerides. This is the first report of an association of a virus with human obesity.

It is unknown if the SMAM-1 antibodies in humans had developed in response to a past infection with the virus or due to a human adenovirus antigenically similar to SMAM-1. These data are in contrast to conventional wisdom that avian adenoviruses do not infect humans and human adenoviruses do not cross-react with avian adenoviruses (15). Experiments described below show that a human adenovirus, Ad-36, can infect chickens and induce adiposity.

Human adenovirus Ad-36. Adenoviruses are naked DNA viruses with icosahedral symmetry and a diameter of 65–80 nm. In humans, adenoviruses are frequently associated with acute upper respiratory tract infections, and they may also cause enteritis and conjunctivitis. Adenoviruses can easily be isolated from nasal swabs or from feces. Adenovirus infections are transmitted via respiratory, fomite, droplet, venereal and fecal-oral routes. There are 50 different types of human adenoviruses listed with the American Type Culture Collection. Adenovirus type 36 (Ad-36) does not cross-react with most other human adenoviruses (29,30); therefore, it is antigeni-

cally unique. Ad-36 was first isolated in 1978 in Germany in the feces of a 6-y-old girl suffering from diabetes and enteritis (30).

In four separate experiments, chickens and mice were inoculated with human adenovirus Ad-36. These animals developed a syndrome of increased adipose tissue and paradoxically low levels of serum cholesterol and triglycerides (9). This syndrome was not seen in the chickens inoculated with avian adenovirus CELO. Sections of the brain and hypothalamus of Ad-36–inoculated animals did not show any overt histopathological changes. Ad-36 DNA could be detected in adipose tissue, but not skeletal muscles of animals, for as long as 16 wk after Ad-36 inoculation [**Table 1** (9)].

Subsequently, to ascertain if blood transfusion from Ad-36–infected chickens could produce adiposity in uninfected animals, four age- and weight-matched groups of chickens, infected donors and recipients (I-D and I-R, respectively) and control donors and recipients (C-D and C-R, respectively) were used (31). At age 4 wk, I-D and C-D were inoculated with Ad-36 or cell culture media, respectively. After 36 h, 200 μL blood from I-D and C-D was drawn and injected into wing veins of I-R and C-R chickens, respectively. Viremia was demonstrated in the transfused blood drawn from the I-D group. Using a capillary electrophoresis assay developed for the purpose (32), Ad-36 DNA was detected in the adipose tissue of the I-D and I-R groups but not in the skeletal muscle. Compared with the C-D group, the I-D group had ~2.5 times and the I-R group had 1.8 times greater visceral fat. The two infected groups (I-D and I-R) also showed a significant reduction in cholesterol, and the I-D group had a significant reduction in serum triglycerides. These data confirmed the previous findings that Ad-36 produces adiposity and paradoxical reductions in serum lipids. In addition, the study fulfilled Koch's postulate by transmitting disease (adiposity) from infected animals (I-D group) to a new set of animals (I-R group).

Human studies. Human serum samples obtained from obese (BMI $\geq$27 kg/m^2) and nonobese volunteers from three different sites (Wisconsin, Florida and New York) were screened for the presence of Ad-36 antibodies using serum neutralization assays. Prevalence of Ad-36 antibodies in three sites pooled together was 5% for the nonobese and 30% for the obese subjects (33,34). At each of the sites, the antibody-positive obese subjects had significantly lower serum cholesterol compared with the antibody-negative obese subjects from the respective site (33,34). Thus, antibody-positive humans had lower serum cholesterol and triglycerides levels, like the animals experimentally infected with Ad-36.

These data show an association of Ad-36 antibodies with human obesity but do not establish a causative relationship. Because of ethical reasons, the definitive experiment of injecting humans with Ad-36 to determine the role of Ad-36 in human obesity is unlikely to ever be conducted. Relevance of Ad-36 to human obesity would continue to be open to question until perhaps the experiments are conducted in a model more relevant to humans. Recent preliminary data have suggested the suitability of two nonhuman primate models, rhesus monkeys and marmosets, to study the adiposity promoting potential of Ad-36 (35,36). More animal and human research is needed to establish the contribution of Ad-36 in human obesity.

Infections and obesity: conjectures. Although a causative role of certain infections in obesity is a relatively novel concept, adipose tissue involvement with modulators and mediators of immune response is well documented. For example, Cousin et al. (37) showed that preadipocytes function like macrophages and possess phagocytic and microbicidal activity. Adipocytes also participate in the immune response. Leptin, an adipocyte-secreted hormone involved in body weight regulation, also enhances proliferation and activation of human circulating T-cells and stimulates cytokine production (38). In addition to leptin-directed modulation of cytokine release, adipocytes themselves secrete various cytokines (39,40) and, in turn, preadipocytes and adipocytes are subject to cytokine-directed modulations (41,42). With such an extensive interaction between the immune system and the adipose tissue, expansion of the latter in response to certain infections is conceivable. For instance, macrophage colony–stimulating factor, which promotes the production of macrophages, is also secreted by adipocytes and, when overexpressed in vivo, induces significant adipose tissue hyperplasia (43). It is unknown if the obesity-promoting pathogens stimulate macrophage colony–stimulating factor production that leads to the growth of adipose tissue.

A body of evidence shows association of obesity with cytokines and markers of inflammation. Elevated levels of interleukin-6 (44) and C-reactive proteins (45) are observed in obese individuals. Interestingly, Duncan et al. (46) showed that markers of inflammation can predict weight gain in middle-aged adults. A 3-y follow-up of >13,000 men and women showed an adjusted odds ratio of a large weight gain (>90th percentile) of 1.65 for those in the highest quartile for baseline fibrinogen levels as compared with the lowest quartile (46). Higher odds ratios for large weight gain were also seen with other markers of inflammation. The authors suggested that a mild inflammatory response process plays a role in stimulation of weight gain (46). The above-mentioned cross-sectional and prospective studies show association of obesity with the presence of a chronic, mild state of inflammation. It remains to be determined if the noted inflammation was in response to certain infections.

TABLE 1

Prevalence of obesity (%) in animals experimentally infected with Ad-36[1]

	Animal model	Control	Ad-36
Experiment 1	Chickens	23.07	69.23*
Experiment 2	Chickens	18.1	63.6*
Experiment 3	Chickens	12.5	70.0*
Experiment 4	Mice	22.22	60.0**

[1] Obesity was defined as greater than the 85th percentile of adiposity of the control group. * $P < 0.02$, ** $P < 0.05$. Table adapted from (9).

CONCLUSION

The role of infections in the etiology of obesity has not been seriously considered until recently. To date, six different pathogens have been implicated in obesity in animal models, but their role in human obesity has not been established conclusively. Among the obesity-promoting pathogens, CDV is closely related to human measles virus. Also, humans show evidence of Borna Disease Virus infections. However, avian adenovirus SMAM-1 is the first virus to be implicated in human obesity. Ad-36 is the first human virus to be implicated in obesity.

Clearly, not every case of obesity is of infectious origin. However, if a few pathogens can cause obesity, there may be more awaiting discovery. These data give a new perspective to

the etiology of obesity and raise the possibility of infection as a contributing factor for obesity in some humans. When such a relationship between pathogens and human obesity is well established, vaccines or antimicrobial agents may be employed to prevent or treat some forms of obesity.

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